Clopidogrel with Aspirin in Acute Minor Stroke or Transient Ischemic Attack

N Engl J Med. 2013 Jul 4;369(1):11-9

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Background

- TIA(transient ischemic attack) and acute minor ischemic stroke are common.
- In China, 3 million new strokes every year, 30% are minor
- TIA are probably 2 million a year
- The risk of subsequent stroke after TIA or minor stroke was 10~20% within 3 months, most of first 2 days.

Background

- The role of antiplatelet therapy for secondary stroke prevention has been well established.
- Aspirin was the only proved antiplatelet for stroke.
- Aspirin and clopidogrel synergistically inhibit platelet aggregation was proved in ACS.
- Large-scale trials showed no benefit of combination aspirin and clopidogrel in stroke.

Background

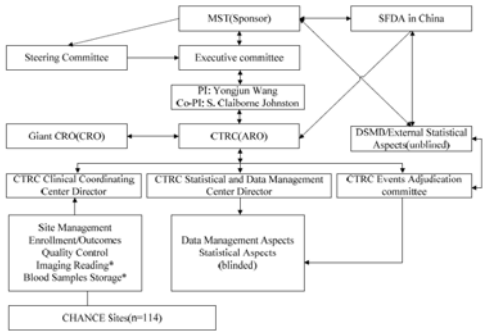
- No study for early, high risk population
- Only three small pilot trails showed benefit of combination therapy.
- Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events (CHANCE) trial

Background

- Hypothesis: 3 months of treatment with a combination of clopidogrel and aspirin would reduce the risk of recurrent stroke, as compared with aspirin alone, among patients with acute high-risk TIA or minor ischemic stroke.

Methods

- Study oversight
- Study population
- Study design
- Study outcome
- Statistic analysis



Study population

- Inclusion criteria:
  - age of 40 years or older
  - acute minor ischemic stroke(NIHSS<4) or TIA(risk score ≥4) and ability to start the study drug within 24 hours after symptom onset
- ABCD score: age, blood pressure, clinical features, duration of TIA, and presence or absence of diabetes, range 0~7 higher score indicated higher risk

Study population

- All patients with possible clinical neurologic events during the follow-up period underwent computed tomography (CT) or magnetic resonance imaging (MRI) of the head.

Study population

- Exclusion criteria:
  - Hemorrhage
  - Major nonischemic brain disease(e.g., vascular malformation, tumor, abscess…)
  - Isolated sensory symptoms (e.g., numbness)
  - Isolated visual changes
  - Isolated dizziness or vertigo
  - Modified Rankin scale(mRS) > 2
  - NIHSS ≥ 4
  - Indication for anticoagulation therapy(atrial fibrillation or prosthetic cardiac valve)

Study population

- Exclusion criteria:
  - History of intracranial hemorrhage
  - Contraindication to clopidogrel or aspirin
  - Long-term antiplatelet drugs or NSAIDs affecting platelet
  - Heparin therapy or oral anticoagulation therapy within 10 days
  - Gastrointestinal bleeding or major surgery within the previous 3 months
  - Planned or probable revascularization within 3 months
  - Planned surgery
  - TIA or minor stroke caused by angiography or surgery

Study population

- Exclusion criteria:
- severe noncardiovascular coexisting condition, with a life expectancy of less than 3 months
- Women plan or pregnancy

Table S1. Inclusion and exclusion criteria

Inclusion criteria
• Adult subjects (male or female ≥ 40 years)
• Acute non-disabling ischemic stroke (NIHSS≤3 at the time of randomization) that can be treated with study drug within 24 hours of symptoms onset. Symptom onset is defined by the "last seen normal" principle.
• TIA (neurological deficit attributed to focal brain ischemia, with resolution of the deficit within 24 hours of symptom onset), that can be treated with study drug within 24 hours of symptoms onset and with moderate-to-high risk of stroke recurrence (ABCD2 score ≥ 4 at the time of randomization). Symptom onset is defined by the "last seen normal" principle.
• Informed consent signed

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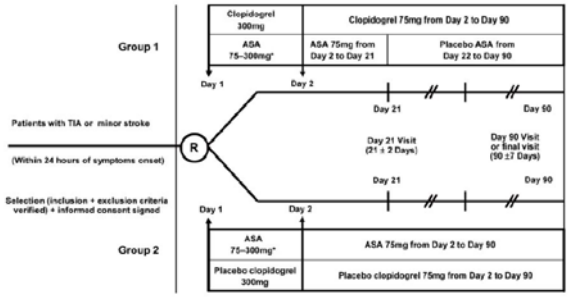
Exclusion Criteria
• Diagnosis of hemorrhage or other pathology, such as vascular malformation, tumor, abscess or other major non-ischemic brain disease (e.g., multiple sclerosis) on baseline head CT or MRI.
• Isolated or pure sensory symptoms (e.g., numbness), isolated visual changes, or isolated dizziness/vertigo without evidence of acute infarction on baseline head CT or MRI.
• mRS > 2 at randomization (pre-morbid historical assessment)
• NIHSS≥ 4 at randomization
• Clear indication for anticoagulation (presumed cardiac source of embolus, e.g., atrial fibrillation, prosthetic cardiac valves known or suspected endocarditis).
• Contraindication to clopidogrel or aspirin.
▪ Known allergy
▪ Severe renal or hepatic insufficiency
▪ Severe cardiac failure, asthma
▪ Hemostatic disorder or systemic bleeding
▪ History of hemostatic disorder or systemic bleeding
▪ History of thrombocytopenia or neutropenia
▪ History of drug-induced hematologic or hepatic abnormalities
▪ Low white blood cell (<2 ×10⁹/l) or platelet count (<100 ×10⁹/l).
▪ Use of thrombolytic within 24 hours prior to randomization
• History of intracranial hemorrhage
• Anticipated requirement for long-term non-study antiplatelet drugs, or NSAIDs affecting platelet function.
• Current treatment (last dose given within 10 days before randomization) with heparin therapy or oral anticoagulation.
• Gastrointestinal bleed or major surgery within 1 months.
• Planned or likely revascularization (any angioplasty or vascular surgery) within the next 3 months (if clinically indicated, vascular imaging should be performed prior to randomization whenever possible)
• Scheduled for surgery or interventional treatment requiring study drug cessation.
• TIA or minor stroke induced by angiography or surgery.
• Severe non-cardiovascular comorbidity with life expectancy < 3 months.
• Women of childbearing age not practicing reliable contraception who do not have a documented negative pregnancy test.
• Currently receiving an investigational drug or device.

Study design

- CHANCE was a randomized, double-blind, placebo controlled clinical trial
- 114 clinical centers
- 5170 patients
- October 2009 to July 2012
- Stratified : <12 hours vs. 12 to 24 hours and location

Study design



Study outcome

- Primary efficacy outcome: new stroke event (ischemic or hemorrhagic) at 90 days
  - sudden onset of a new focal neurologic deficit
  - clinical or imaging evidence of infarction lasting 24 hours or more and not attributable to a nonischemic cause
  - neuroimaging evidence of new brain infarction
  - rapid worsening of an existing focal neurologic deficit
  - brain parenchyma or subarachnoid space with associated neurologic symptoms
  - mRS >2

Study outcome

- Primary safety outcome: moderate to severe bleeding event
  - Severe hemorrhage
    - fatal
    - intracranial hemorrhage
    - hemodynamic compromise required blood or fluid replacement, inotropic support, or surgical intervention
  - Moderate hemorrhage
    - required transfusion of blood
- Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries(GUSTO)

Study outcome

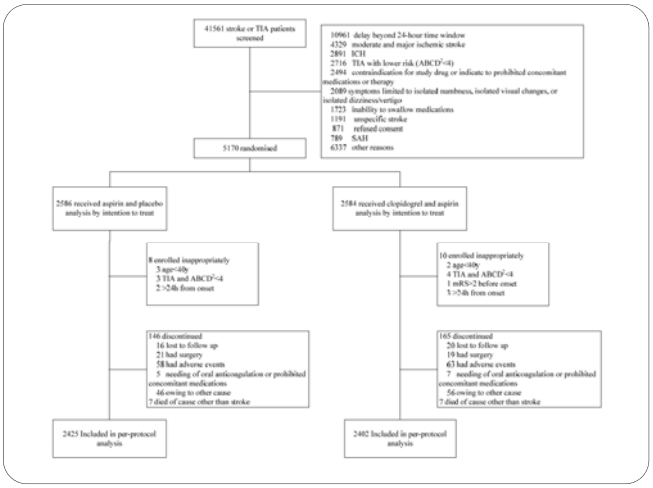
- Secondary efficacy outcomes: new clinical vascular event
  - Ischemic stroke
  - Hemorrhagic stroke,
  - Myocardial infarction
  - Vascular death
    - Stroke (ischemic or hemorrhagic)
    - Systemic hemorrhage,
    - Myocardial infarction
    - Congestive heart failure
    - Pulmonary embolism
    - Sudden death
    - Arrhythmia

Statistic analysis

- 5100 patients, 90% power to detect a relative risk reduction of 22% in the clopidogrel–aspirin group, with a two-sided type I error of 0.05, assuming an event rate of 14% in the aspirin group and a 5% overall rate of withdrawal
- Baseline characteristics of the patients in the two study groups
- Cox proportional-hazards model

Statistic analysis

- Multiple events, first event was used
- If study termination or death but no stroke event patients were censored
- Treatment-by-subgroup interaction effect
- All tests were two-sided, and a P value of 0.05



Results

- Median age: 62 y/o
- Female: 33.8%
- History of hypertension: 65.7%
- Diabetes: 21.1%
- Smoke: 43.0%
- Median time of onset to qualifying: 13 hrs
- TIA: 1445 patients (27.9%)
- 36 patients (0.7%)20 in the clopidogrel–aspirin group and 16 in the aspirin group lost follow up
- 165 patients (6.4%) in the clopidogrel–aspirin group and 146 (5.6%) in the aspirin group discontinued drug

Results

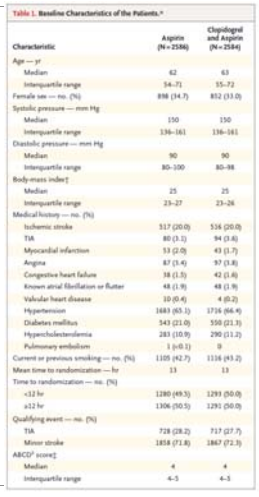


Table 1. Baseline Characteristics of the Patients.*

Characteristic	Aspirin (N = 2586)	Clopidogrel and Aspirin (N = 2584)
Age — yr		
Median	62	63
Interquartile range	54–71	55–72
Female sex — no. (%)	898 (34.7)	852 (33.0)
Systolic pressure — mm Hg		
Median	150	150
Interquartile range	136–161	136–161
Diastolic pressure — mm Hg		
Median	90	90
Interquartile range	80–100	80–98
Body-mass index†		
Median	25	25
Interquartile range	23–27	23–26
Medical history — no. (%)		
Ischemic stroke	517 (20.0)	536 (20.0)
TIA	80 (3.1)	94 (3.6)
Myocardial infarction	53 (2.0)	43 (1.7)
Angina	87 (3.4)	97 (3.8)
Congestive heart failure	38 (1.5)	42 (1.6)
Known atrial fibrillation or flutter	48 (1.9)	48 (1.9)
Valvular heart disease	10 (0.4)	4 (0.2)
Hypertension	1683 (65.1)	1716 (66.4)
Diabetes mellitus	543 (21.0)	550 (21.3)
Hypercholesterolemia	283 (10.9)	290 (11.2)
Pulmonary embolism	1 (<0.1)	0
Current or previous smoking — no. (%)	1105 (42.7)	1116 (43.2)
Mean time to randomization — hr	13	13
Time to randomization — no. (%)		
<12 hr	1280 (49.5)	1293 (50.0)
≥12 hr	1306 (50.5)	1291 (50.0)
Qualifying event — no. (%)		
TIA	728 (28.2)	717 (27.7)
Minor stroke	1858 (72.8)	1867 (72.3)
ABCD² score‡		
Median	4	4
Interquartile range	4–5	4–5

Results

- Baseline features:
  - Medication taken within 24HR before hospital admission, Dipyridamole (P=0.04, control group)
  - LABORATORY TESTS AT ADMISSION (normal), Hb(P=0.05, control group)

Table 2. Efficacy and Safety Outcomes.

Outcome	Aspirin (N=2586) Patients with Event no.	Aspirin (N=2586) Event Rate %	Clopidogrel and Aspirin (N=2584) Patients with Event no.	Clopidogrel and Aspirin (N=2584) Event Rate %	Hazard Ratio (95% CI)	P Value
Primary outcome						
Stroke	303	11.7	212	8.2	0.68 (0.57–0.81)	<0.001
Secondary outcomes						
Stroke, myocardial infarction, or death from cardiovascular causes	307	11.9	216	8.4	0.69 (0.58–0.82)	<0.001
Ischemic stroke	295	11.4	204	7.9	0.67 (0.56–0.81)	<0.001
Hemorrhagic stroke	8	0.3	8	0.3	1.01 (0.38–2.70)	0.98
Myocardial infarction	2	0.1	3	0.1	1.44 (0.24–8.63)	0.69
Death from cardiovascular causes	5	0.2	6	0.2	1.16 (0.35–3.79)	0.81
Death from any cause	10	0.4	10	0.4	0.97 (0.40–2.33)	0.94
Transient ischemic attack	47	1.8	39	1.5	0.82 (0.53–1.26)	0.36
Safety outcomes						
Bleeding*						
Severe	4	0.2	4	0.2	0.94 (0.24–3.79)	0.94
Moderate	4	0.2	3	0.1	0.73 (0.16–3.26)	0.68
Mild	19	0.7	30	1.2	1.57 (0.88–2.79)	0.12
Any bleeding	41	1.6	60	2.3	1.41 (0.95–2.10)	0.09
Fatal or disabling stroke	177	6.8	135	5.2	0.75(0.60-0.94)	0.01

Results

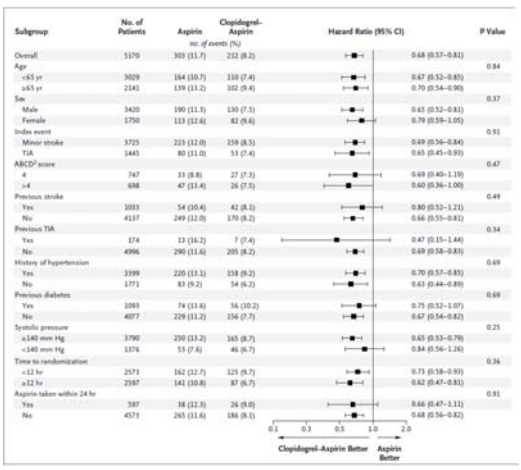


Table S4. Adverse events (36 missing follow up) within 90 days.

Outcome	Placebo plus Aspirin (n=2570)	Clopidogrel plus Aspirin (n=2564)	P Value
SAE			
death	10(0.4%)	10(0.4%)	0.34
Hemorrhagic stroke	7(0.3%)	6(0.2%)	
others	4(0.2%)	11(0.4%)	
AE			
Skin Disorders: rash, itchy skin, dermatitis, psoriasis	10(0.4%)	13(0.5%)	0.53
Digestive System Symptoms: gastrointestinal discomfort(nausea, vomiting), diarrhea, abdominal pain, gastritis, ulcer	13(0.5%)	14(0.6%)	0.84
Respiratory System Symptoms: respiratory tract infections, dyspnea, etc.	11(0.4%)	9(0.4%)	0.66
Gastrointestinal Haemorrhage	4(0.2%)	9(0.4%)	0.16
Subcutaneous Hemorrhage/Dermatorrhagia: ecchymosis, hemorrhagic spot, hematoma	7(0.3%)	15(0.6%)	0.09
Gingival Bleeding/Epistaxis	9(0.4%)	8(0.3)	0.81
Asymptomatic Intracranial Microhemorrhage*	6(0.2%)	6(0.2%)	1.00
Cardiovascular System Symptoms: arrhythmia, acute coronary syndrome, cardiac dysfunction, etc	16(0.6%)	21(0.8%)	0.40
Tumor/Cancer/Occupying Lesion	7(0.3%)	10(0.4%)	0.46
Others	41(1.6%)	39(1.5%)	0.83

Discussion

- Addition of clopidogrel to aspirin within 24 hours after symptom onset reduced the risk of subsequent stroke by 32.0%, absolute risk reduction of 3.5%.
- Number needed to treat to prevent one stroke over a period of 90 days: 29
- Combination therapy was not associated with an increased incidence of hemorrhage despite worrisome trend in overall bleeding

Discussion

- The results differ from other trails
- Targeted a population at particularly high risk
- Previous trials: patients with more severe strokes, not enroll patients in the first hours

Discussion

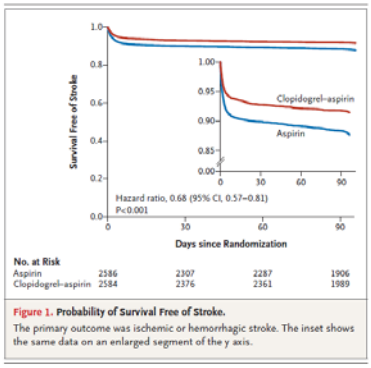


Figure 1. Probability of Survival Free of Stroke.
The primary outcome was ischemic or hemorrhagic stroke. The inset shows the same data on an enlarged segment of the y axis.

Discussion

- In China, 150 to 250 deaths from stroke per 100,000 persons per year, five times as high as in U.S.
- Secondary prevention practices are less rigorous in China
- Higher incidence of large-artery intracranial atherosclerosis
- Higher prevalence of genetic polymorphisms that affect the metabolism of clopidogrel
- POINT trail

Discussion

- Several common clinical conditions mimic TIA
  - Seizures
  - Migraine
  - Peripheral vertigo
  - Syncope
  - Anxiety
- TIA with high ABCD score
- The study findings may not apply to other populations

Conclusion

- Patients with high-risk TIA or minor ischemic stroke who are initially seen within 24 hours after symptom onset, treatment with clopidogrel plus aspirin for 21 days, followed by clopidogrel alone for a total of 90 days, is superior to aspirin alone in reducing the risk of subsequent stroke events.
- The combination of clopidogrel with aspirin did not cause more hemorrhagic events in this patient population than aspirin alone.